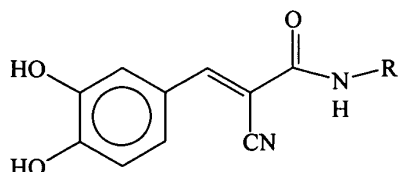


Oshero et al., J. Biol. Chem., 268, 11,134-142 (1993), disclose tyrphostins that inhibit EGFR/HER1 and HER2. The benzylidene malononitrile or tyrphostin compounds disclosed in the Oshero et al. article, in particular, those in Tables I, II, III, and IV are incorporated herein by reference and are set forth generically in the following structure:

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wherein R is a cyclohexane, benzene, or benzene alkyl having 1-4 carbons in the alkyl, which benzene can be optionally substituted with Cl, OH, or CH₃.

In the Claims:

⌈ Please delete claims 1-35 and add the following new claims: ⌋

36. (New) A method of inhibiting growth of a refractory tumor that has failed or been resistant to treatment comprising administering to a human an epidermal growth factor receptor (EGFR) antagonist and a chemotherapeutic agent, wherein administration is effective to inhibit growth of the refractory tumor.

37. (New) The method according to claim 36, wherein the refractory tumor overexpresses EGFR.

38. (New) The method according to claim 36, wherein the refractory tumor is a refractory tumor of the breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, or liver.

39. (New) The method according to claim 36, wherein the refractory tumor is a refractory tumor of the colon or head and neck.

40. (New) The method according to claim 36, wherein the refractory tumor is a refractory squamous cell tumor.

41. (New) The method according to claim 36, wherein the EGFR antagonist is administered intravenously.

42. (New) The method according to claim 36, wherein the EGFR antagonist is administered orally.

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43. (New) The method according to claim 36, wherein the EGFR antagonist is administered prior to administration of the chemotherapeutic agent.

44. (New) The method according to claim 36, wherein the EGFR antagonist is administered at a dose of about 10 to about 500 mg/m² weekly.

45. (New) The method according to claim 36, wherein the EGFR antagonist inhibits stimulation of EGFR by its ligand.

46. (New) The method according to claim 45, wherein the EGFR antagonist inhibits binding of EGFR to its ligand.

47. (New) The method according to claim 45, wherein the EGFR antagonist binds EGFR externally.

48. (New) The method according to claim 45, wherein the EGFR antagonist binds EGFR internally.

49. (New) The method according to claim 45, wherein the EGFR antagonist inhibits binding of ATP to EGFR.

50. (New) The method according to claim 45, wherein the EGFR antagonist competes with ATP for EGFR.

51. (New) The method according to claim 45, wherein the EGFR antagonist inhibits EGFR phosphorylation.

52. (New) The method according to claim 45, wherein the EGFR antagonist inhibits EGFR tyrosine kinase activity.

53. (New) The method according to claim 36, wherein the EGFR antagonist comprises an antibody, or functional equivalent thereof, specific for EGFR.

54. (New) The method according to claim 53, wherein the antibody comprises a constant region of a human antibody.

55. (New) The method according to claim 54, wherein the antibody is a chimeric antibody comprising a variable region of a mouse antibody.

56. (New) The method according to claim 54, wherein the antibody is a humanized antibody comprising a variable region having complementarity-determining regions (CDRs) of a mouse antibody and framework regions of a human antibody.

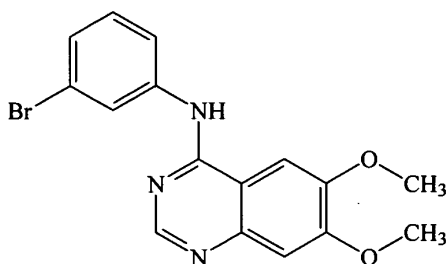
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57. (New) The method according to claim 54, wherein the antibody is a human antibody comprising a variable region of a human antibody.

58. (New) The method according to claim 54, wherein the antibody is administered at a dose sufficient to saturate EGFR.

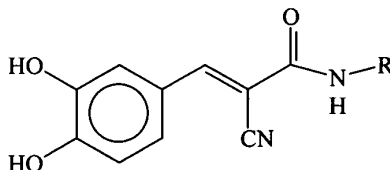
59. (New) The method according to claim 36, wherein the EGFR antagonist comprises a small molecule.

60. (New) The method according to claim 59, wherein the small molecule comprises a compound, PD 153035, having the following structure:



61. (New) The method according to claim 59, wherein the small molecule comprises a benzylidene malononitrile or tyrphostin compound.

62. (New) The method according to claim 61, wherein the benzylidene malononitrile compound comprises the following structure:

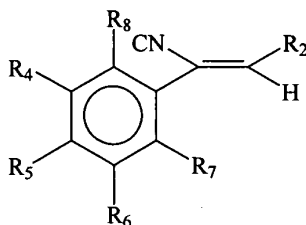


wherein R is a cyclohexane, benzene, or benzene alkyl having 1-4 carbons in the alkyl, which benzene can be optionally substituted with Cl, OH, or CH₃.

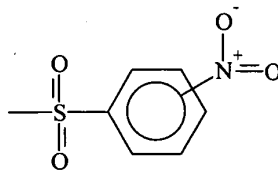
63. (New) The method according to claim 59, wherein the small molecule comprises a styryl substituted heteroaryl compound.

64. (New) The method according to claim 63, wherein the styryl substituted heteroaryl compound comprises a monocyclic ring with 1 or 2 heteroatoms or a bicyclic ring with from 1 to about 4 heteroatoms, which can be optionally substituted or polysubstituted.

65. (New) The method according to claim 63, wherein the styryl substituted heteroaryl compound comprises the following structure:



wherein R is H, alkyl, or aralkyl; R₂ is an about 8- to about 12-membered bicyclic aryl ring including 1 to about 4 N, O or S atoms or 1 to about 4 N-oxide groups, which ring can be optionally substituted with 1 to about 3 R₉ substituents having no common points of attachment to said ring; R₄, R₅, R₆, R₇, and R₈ are each independently H, CN, alkyl, halo, OR, CHO, COOH, NRR or an N-oxide thereof, NO₂, NHCOCH₃, SR, CF₃, CH=CHCOOH, CHCO(CH₂)₂COOH, heterocyclic, heteroaryl, or the following structure:

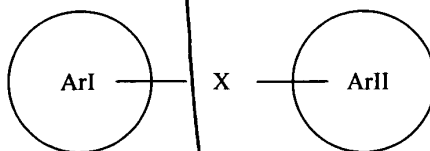


66. (New) The method according to claim 59, wherein the small molecule comprises a tricyclic pyrimidine compound.

67. (New) The method according to claim 66, wherein the tricyclic pyrimidine compound comprises a 4-(3-bromoanilino)benzothieno[3,2-d]pyrimidine; 4-(3-bromoanilino)-8-nitrobenzothieno[3,2-d]pyrimidine; 8-amino-4-(3-bromoanilino)benzothieno[3,2-d]pyrimidine or 4-(3-bromoanilino)-8-methoxybenzothieno[3,2-d]pyrimidine.

68. (New) The method according to claim 59, wherein the small molecule comprises a bis mono or bicyclic aryl, heteroaryl, carbocyclic, or heterocarbocyclic compound.

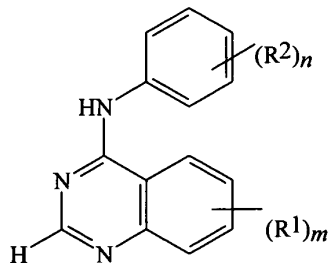
69. (New) The method according to claim 59, wherein the small molecule comprises a compound having the following structure:



wherein ArI and ArII are independently a substituted or unsubstituted mono- or bicyclic ring, said rings optionally substituted with 1 to about 3 R groups; X is (CHR₁)₀₋₄ or (CHR₁)_m-Z-(CHR₁)_n, which Z is O, NR', S, SO, or SO₂, m and n are 0-3 and m+n=0-3 and R₁ and R' are independently H or alkyl, or a pharmaceutically acceptable salt thereof.

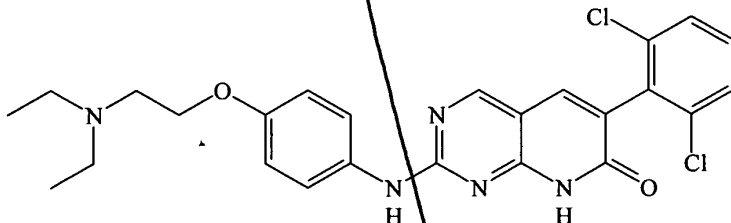
70. (New) The method according to claim 59, wherein the small molecule comprises a quinazoline derivative.

71. (New) The method according to claim 70, wherein the quinazoline derivative comprises a compound having the following structure:



wherein m is 1, 2 or 3 and each R^1 includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkylenedioxy and n is 1 or 2 and each R^2 includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl; or a pharmaceutically acceptable salt thereof.

72. (New) The method according to claim 59, wherein the small molecule comprises a compound, PD 166285, having the following structure:



73. (New) The method according to claim 36, wherein the chemotherapeutic agent comprises amifostine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozocin, cyclophosphamide, carmustine, lomustine, doxorubicin, doxorubicin lipo, gemcitabine, daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin, paclitaxel, docetaxel, aldesleukin, asparaginase, busulfan, carboplatin, cladribine, camptothecin, CPT-11, 10-hydroxy-7-ethyl-camptothecin (SN38), dacarbazine, floxuridine, fludarabine, hydroxyurea, ifosfamide, idarubicin, mesna, interferon alpha, interferon beta, irinotecan, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, or chlorambucil or a combination thereof.

74. (New) The method according to claim 36, wherein the chemotherapeutic agent comprises cisplatin, doxorubicin, paclitaxel, Irinotecan (CPT-11), or topotecan, or a combination thereof.

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75. (New) The method according to claim 36, wherein the chemotherapeutic agent is administered at a dose of about 69 to about 125 mg/m² weekly.

76. (New) The method according to claim 36, wherein the method further comprises administering an adjuvant.

77. (New) The method according to claim 36, wherein the method further comprises administering radiation.

78. (New) The method according to claim 77, wherein the radiation is from a source external to the human.

79. (New) The method according to claim 77, wherein the radiation is from a source internal to the human.

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80. (New) The method according to claim 77, wherein the radiation is administered from about 2 to about 80 Gy.

81. (New) A method of inhibiting growth of a refractory tumor that has failed or been resistant to treatment comprising administering to a human an epidermal growth factor receptor (EGFR) antagonist and radiation, wherein administration is effective to inhibit growth of the refractory tumor.

82. (New) The method according to claim 81, wherein the refractory tumor overexpresses EGFR.

83. (New) The method according to claim 81, wherein the refractory tumor is a refractory tumor of the breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, or liver.

84. (New) The method according to claim 81, wherein the refractory tumor is a refractory tumor of the colon or head and neck.

85. (New) The method according to claim 81, wherein the refractory tumor is a refractory squamous cell tumor.

86. (New) The method according to claim 81, wherein the EGFR antagonist is administered intravenously.

87. (New) The method according to claim 81, wherein the EGFR antagonist is administered orally.

88. (New) The method according to claim 81, wherein the EGFR antagonist is administered prior to administration of radiation.

89. (New) The method according to claim 81, wherein the EGFR antagonist is administered at a dose of about 10 to about 500 mg/m² weekly.

90. (New) The method according to claim 81, wherein the EGFR antagonist inhibits stimulation of EGFR by its ligand.

91. (New) The method according to claim 89, wherein the EGFR antagonist inhibits binding of EGFR to its ligand.

92. (New) The method according to claim 89, wherein the EGFR antagonist binds EGFR externally.

93. (New) The method according to claim 89, wherein the EGFR antagonist binds EGFR internally.

94. (New) The method according to claim 89, wherein the EGFR antagonist inhibits binding of ATP to EGFR.

95. (New) The method according to claim 89, wherein the EGFR antagonist competes with ATP for EGFR.

96. (New) The method according to claim 89, wherein the EGFR antagonist inhibits EGFR phosphorylation.

97. (New) The method according to claim 89, wherein the EGFR antagonist inhibits EGFR tyrosine kinase activity.

98. (New) The method according to claim 81, wherein the EGFR antagonist comprises an antibody, or functional equivalent thereof, specific for EGFR.

99. (New) The method according to claim 97, wherein the antibody comprises a constant region of a human.

100. (New) The method according to claim 104, wherein the antibody is a chimeric antibody comprising a variable region of a mouse.

101. (New) The method according to claim 104, wherein the antibody is a humanized antibody comprising a variable region having complementarity-determining regions (CDRs) of a mouse and framework regions of a human.

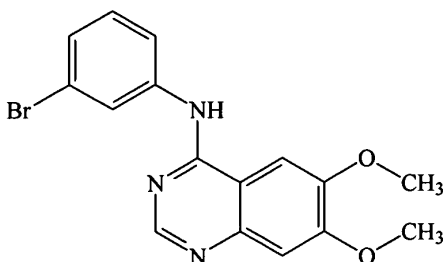
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102. (New) The method according to claim 104, wherein the antibody is a human antibody comprising a variable region of a human.

103. (New) The method according to claim 104, wherein the antibody is administered at a dose effective to saturate EGFR.

104. (New) The method according to claim 81, wherein the EGFR antagonist comprises a small molecule.

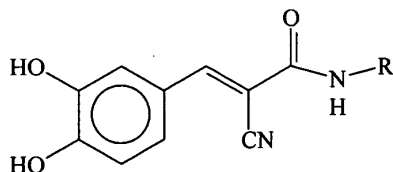
105. (New) The method according to claim 104, wherein the small molecule comprises a compound, PD 153035, having the following structure:



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106. (New) The method according to claim 104, wherein the small molecule comprises a benzylidene malononitrile or tyrphostin compound.

107. (New) The method according to claim 106, wherein the benzylidene malononitrile compound comprises the following structure:

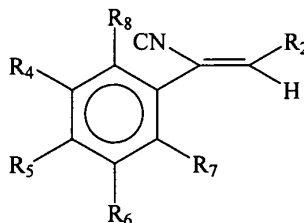


wherein R is a cyclohexane, benzene, or benzene alkyl having 1-4 carbons in the alkyl, which benzene can be optionally substituted with Cl, OH, or CH₃.

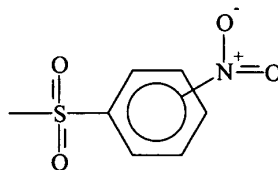
108. (New) The method according to claim 104, wherein the small molecule comprises a styryl substituted heteroaryl compound.

109. (New) The method according to claim 108, wherein the styryl substituted heteroaryl compound comprises a monocyclic ring with 1 or 2 heteroatoms or a bicyclic ring with from 1 to about 4 heteroatoms, which can be optionally substituted or polysubstituted.

110. (New) The method according to claim 108, wherein the styryl substituted heteroaryl compound comprises the following structure:



wherein R is H, alkyl, or aralkyl; R₂ is an about 8- to about 12-membered bicyclic aryl ring including 1 to about 4 N, O or S atoms or 1 to about 4 N-oxide groups, which ring can be optionally substituted with 1 to about 3 R₉ substituents having no common points of attachment to said ring; R₄, R₅, R₆, R₇, and R₈ are each independently H, CN, alkyl, halo, OR, CHO, COOH, NRR or an N-oxide thereof, NO₂, NHCOCH₃, SR, CF₃, CH=CHCOOH, CHCO(CH₂)₂COOH, heterocyclic, heteroaryl, or the following structure:



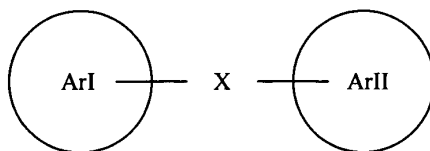
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111. (New) The method according to claim 104, wherein the small molecule comprises a tricyclic pyrimidine compound.

112. (New) The method according to claim 111, wherein the tricyclic pyrimidine compound comprises a 4-(3-bromoanilino)benzothieno[3,2-d]pyrimidine; 4-(3-bromoanilino)-8-nitrobenzothieno[3,2-d]pyrimidine; 8-amino-4-(3-bromoanilino)benzothieno[3,2-d]pyrimidine or 4-(3-bromoanilino)-8-methoxybenzothieno[3,2-d]pyrimidine.

113. (New) The method according to claim 104, wherein the small molecule comprises a bis mono or bicyclic aryl, heteroaryl, carbocyclic, or heterocarbocyclic compound.

114. (New) The method according to claim 104, wherein the small molecule comprises a compound having the following structure:

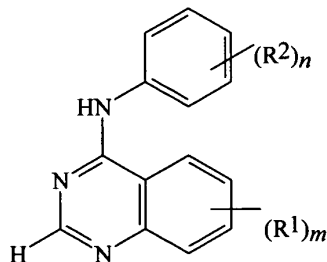


wherein ArI and ArII are independently a substituted or unsubstituted mono- or bicyclic ring, said rings optionally substituted with 1 to about 3 R groups; X is (CHR₁)₀₋₄ or (CHR₁)_m-Z-(CHR₁)_n, which Z is O, NR', S, SO, or SO₂, m

and n are 0-3 and $m+n=0-3$ and R_1 and R' are independently H or alkyl, or a pharmaceutically acceptable salt thereof.

115. (New) The method according to claim 104, wherein the small molecule comprises a quinazoline derivative.

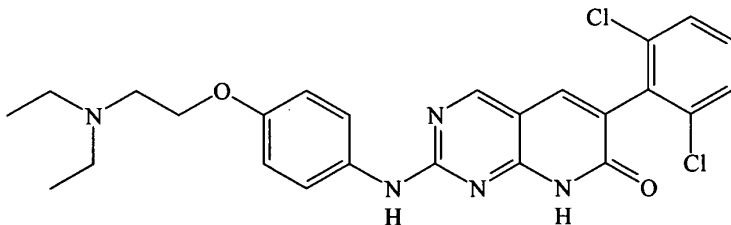
116. (New) The method according to claim 115, wherein the quinazoline derivative comprises a compound having the following structure:



wherein m is 1, 2 or 3 and each R^1 includes hydroxy, amino, carboxy, carbamoyl, ureido, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-[(1-4C)alkyl]carbamoyl, hydroxyamino, (1-4C)alkoxyamino, (2-4C)alkanoyloxyamino, trifluoromethoxy, (1-4C)alkyl, (1-4C)alkoxy and (1-3C)alkylenedioxy and n is 1 or 2 and each R^2 includes hydrogen, hydroxy, halogeno, trifluoromethyl, amino, nitro, cyano and (1-4C)alkyl; or a pharmaceutically acceptable salt thereof.

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117. (New) The method according to claim 104, wherein the small molecule comprises a compound, PD 166285, having the following structure:



118. (New) The method according to claim 81, wherein the radiation is from a source external to the human.

119. (New) The method according to claim 81, wherein the radiation is from a source internal to the human.

120. (New) The method according to claim 81, wherein the radiation is administered from about 2 to about 80 Gy.

121. (New) The method according to claim 81, wherein the method further comprises administering an adjuvant.

122. (New) The method according to claim 81, wherein the method further comprises administering a chemotherapeutic agent.

123. (New) The method according to claim 122, wherein the chemotherapeutic agent comprises amifostine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozocin, cyclophosphamide, carmustine, lomustine, doxorubicin, doxorubicin lipo, gemcitabine, daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin, paclitaxel, docetaxel, aldesleukin, asparaginase, busulfan, carboplatin, cladribine, camptothecin, CPT-11, 10-hydroxy-7-ethyl-camptothecin (SN38), dacarbazine, floxuridine, fludarabine, hydroxyurea, ifosfamide, idarubicin, mesna, interferon alpha, interferon beta, irinotecan, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, or chlorambucil or a combination thereof.

124. (New) The method according to claim 122, wherein the chemotherapeutic agent comprises cisplatin, doxorubicin, paclitaxel, Irinotecan (CPT-11), or topotecan, or a combination thereof.

125. (New) The method according to claim 122, wherein the chemotherapeutic agent is administered at a dose of about 69 to about 125 mg/m² weekly.

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126. (New) A method of inhibiting growth of a head and neck squamous cell refractory tumor that has failed or been resistant to treatment comprising administering to a human a chimeric antibody that is specific for epidermal growth factor receptor (EGFR) and cisplatin, wherein administration is effective to inhibit growth of the head and neck squamous cell refractory tumor.

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127. (New) A method of inhibiting growth of a refractory tumor of the colon that has failed or been resistant to treatment comprising administering to a human a chimeric antibody that specific for epidermal growth factor receptor (EGFR) and Irinotecan (CPT-11), wherein administration is effective to inhibit growth of the refractory tumor of the colon.

In the Abstract:

Please replace the Abstract and the following:

A method of inhibiting growth of a refractory tumor that has failed or been resistant to treatment comprising administering to a human an epidermal

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growth factor receptor (EGFR) antagonist and an antineoplastic agent, such as a chemotherapeutic agent or radiation, wherein administration is effective to inhibit growth of the refractory tumor.
